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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

The Contribution of 3 Tesla MRI to the Preoperative Assessment of Breast Cancer

Meme Kanserinin Operasyon Öncesi Değerlendirilmesinde 3 Tesla Magnetik Rezonans Görüntülemenin Katkısı

Sena Ünal, Ebru Düşünceli Atman, Elif Peker, İlhan Erden, Umman Sanlıdilek

Ankara University Faculty of Medicine, Department of Radiology, Ankara, Türkiye

Abstract

Objectives: To compare magnetic resonance imaging (MRI) findings with postoperative pathological results and to show the effects of MRI on surgical procedures.

Materials and Methods: In this study 31 breast cancer patients whose diagnosis had been proven histopatologically and examined with breast MRI were evaluated retrospectively. The size of the tumor, additional foci in the same breast, the existence of tumor in the other breast, extension to the chest wall and axillary lymph node metastasis were noted. These findings were compared with postoperative histopathological findings.

Results: In 10 patients multifocal disease was identified but only in 3 patients it was proven pathologically. In 1 patient MRI could not identify the additional foci [sensitivity 66%, specificity 71%, positive predictive value (PPV) 20%, negative predictive value (NPV) 95%]. In 2 patients MRI found multicentric foci and they were confirmed with pathology. Out of 6 patients with suspicious findings in the contralateral breast, 1 patient was diagnosed as cancer (sensitivity 100%, specificity 83%, PPV 17%, NPV 100%). Thirteen patients were evaluated as positive for axillary lymph node involvement. One of them did not have axillary lymph node metastasis in the pathology specimens. In 1 patient MRI could not identify the axillary lymph node metastasis (sensitivity 92%, specificity 94%, PPV 92%, NPV 94%). Compared to histopathological measurements, we obtained a high reliability ratio (88%) for the lesion sizes.

Conclusion: MRI can be used to exclude additional foci in patients who have high risks for multifocal and contralateral disease. MRI may reveal false positive results and therefore the diagnosis must be proven with pathology before surgery.

Key Words: Breast Cancer, Magnetic Resonance Imaging, Preoperative MRI

Öz

Amaç: Bu çalışmanın amacı, yeni tanı almış meme kanserli hastalarda operasyon öncesi manyetik rezonans görüntüleme (MRG) bulguları ile patoloji sonuçlarını karşılaştırmak ve MRG bulgularının cerrahi tedaviye etkisini ortaya koymaktır.

Gereç ve Yöntem: Meme kanseri tanısı histopatolojik olarak doğrulanmış ve preoperatif olarak meme MRG yapılmış 31 kadın hasta retrospektif olarak değerlendirildi. MRG'de tümörün boyutu, aynı memede ek odak varlığı, karşı memede tümör varlığı, göğüs duvarı invazyonu olup olmadığı ve aksiller patolojik özellikte lenf nodu varlığı incelendi. Bulgular cerrahi sonrası elde edilen patoloji sonuçları ile karşılaştırıldı.

Bulgular: Patoloji spesmenlerindeki ölçümlerle karşılaştırıldığında MRG'de lezyon boyutlarının yüksek güvenilirlik oranı (%88) ile saptandığı görüldü. Hastaların 10'u MRG'de multifokal odak var olarak değerlendirildi. Tüm hastaların sadece 3'ünde patolojik olarak multifokal odak varlığı doğrulandı. Bu hastaların 1'inde MRG'de lezyon saptanamadı [duyarlılık %67, özgüllük %71, pozitif prediktif değer (PPD) %20, negatif prediktif değer (NPD) %95]. MRG'de multisentrik olarak değerlendirilen 2 hastada tanı patolojik olarak doğrulandı. Karşı memede malignite açısından şüpheli lezyon saptanan 6 hastanın 1'inde kanser varlığı doğrulandı (duyarlılık %100, özgüllük %83, PPD %17, NPD %100). MRG'de 13 hasta patolojik aksiller lenf nodu yönünden pozitif olarak değerlendirildi. Bütün hastaların 13'ünde patoloji sonuçlarında aksiller metastaz saptandı. Bir hastada MRG'de aksiller metastaz saptanamadı (duyarlılık %92, özgüllük %94, PPD %92, NPD %94).

Yazışma Adresi/Address for Correspondence: Sena Ünal, Ankara University Faculty of Medicine, Department of Radiology, Ankara, Türkiye
Tel.: +90 536 971 65 60 **E-posta:** drsenaunal@gmail.com **ORCID ID:** orcid.org/0000-0001-6680-0789
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Öz

Sonuç: Meme MRG meme kanserli hastaların cerrahi öncesinde değerlendirilmesinde tümör boyutunun belirlenmesinde ve aksiller lenf nodu tutulumunun değerlendirilmesinde güvenilir sonuçlar vermektedir. Multifokalite ve kontralateral malignite olasılığı yüksek hastalarda ek odak varlığının dışlanmasında kullanılabilir. Ek odakların tespitinde yalancı pozitif sonuçlara neden olabileceğinden cerrahi öncesi histopatolojik örnekleme ile tanı doğrulanmalıdır.

Anahtar Kelimeler: Meme Kanseri, Manyetik Rezonans Görüntüleme, Preoperatif MRG

Introduction

Prognosis and treatment protocol of breast cancer mostly depends on stage of the cancer. Staging helps determining the surgical method, chemotherapy, hormonal therapy or radiation therapy and axillary lymph node dissection. Preoperative staging is made with combination of physical examination and radiological findings (1).

Breast magnetic resonance imaging (MRI) is an important imaging modality in detection and assessment of benign and malign breast lesions and in assessment of preoperative tumor size (2). Preoperative local staging, searching of primary tumor for cancers with unknown primary, differentiation between local recurrence and scar tissue after breast-conserving surgery (BCS), early breast cancer detection for patients with high risk, monitoring during neoadjuvant chemotherapy, follow-up of patients with breast prosthesis are indications for breast MRI. Preoperative local staging is one of the most important indications of usage of breast MRI. MRI is the most sensitive radiological modality for detecting breast cancer. Measuring of tumor size, detecting of extensive intraductal component, searching for multifocal and multicentric focus and contralateral tumor, detecting of lymph node involvement are the purposes of preoperative local staging with breast MRI (3).

Breast-conserving surgery is preferred in early stages of breast cancer. There is no significant difference for survival rates of early stage breast cancer between patients treated with BCS and patients treated with mastectomy. Tumor size and presence of additional focus are important to determine the surgical method. Detecting additional lesions may lead to wider excisions (4). MRI is the most sensitive imaging modality for detecting breast cancer and it is more sensitive than conventional imaging modalities to assess tumor size and multifocality and multicentricity (5,6). Therefore, using preoperative MRI can help surgeons for better surgical plans. It may help to reduce reexcisions by detecting additional focus preoperatively (7).

Besides its advantages for detecting lesions with high sensitivity, MRI may have some disadvantages. False positive results may be obtained in detecting additional lesions due to this feature and may lead to unnecessary surgeries or wider excisions (8,9). Investigating these additional lesions may also cause increased anxiety in patients, additional burden on healthcare system and surgical delays (10).

The aim of this study is to compare MRI findings with postoperative pathological results and to show the effects of MRI on surgical procedures.

Materials and Methods

Patients

Retrospectively, 44 patients diagnosed as breast cancer and underwent dinamic contrast-enhanced breast MRI between October 2012 and December 2015 were evaluated. Patients with no histopathological confirmation and patients who had neoadjuvant chemotherapy excluded from the study. Having cytological or histopathological proven breast cancer with fine needle aspiration biopsy, tru-cut biopsy or excisional biopsy and having breast MRI preoperatively were determined as inclusion criteria. Two patients had neoadjuvant chemotherapy, one patient was accepted as inoperable and ten patients were out of follow-up. Of the 44 patients 31 meeting these criteria were included to the study.

The Institutional Review Board of Ankara University Faculty of Medicine approved this retrospective study protocol and waived informed consent (approval no: 19-798-15, date: 11.12.2015).

MRI Protocol and Evaluation of Images

All patients underwent MRI at 3 Tesla (Siemens Magnetom Verio syngo MR B17, Erlangen, Germany) using bilateral 16-channel breast coil. Patients were placed in prone position. Images were obtained at axial plane using TIRM TRA P3 (TR/TE: 3500 ms/70 ms, slice thickness 4 mm, slice number 34, with fat suppression), T1 weighted TSE TRA P2 (TR/TE: 650 ms/11 ms, slice thickness 4 mm, slice number 34, without fat suppression), T2 weighted TRA SPC 3D (TR/TE: 1200 ms/204 ms, slice thickness 1 mm, slice number 144, without fat suppression), T1 weighted TSE TRA FS (TR/TE: 850 ms/11 ms, slice thickness 4 mm, slice number 34, with fat suppression), diffusion weighted (TR/TE: 6600 ms/85 ms, slice thickness 4 mm, slice number 34, with fat suppression, b-value 1: 50 s/mm^2, b-value 2: 400 s/mm^2, b-value 3: 800 s/mm^2) and T1 weighted FL3D TRA DYNAVIEWS SPAIR (TR/TE: 4.32 ms/1.57 ms, slice thickness 1 mm, slice number

144, with fat suppression). The field of view was 340x340 mm. The contrast agent (gadolinium) administered at a dose of 0.1 mmol/kg by intravenous injection at a rate of 2.5 mL/s with an automatic injector. After contrast agent injection 1 minute lasting 6 dynamic images were obtained. For dynamic images a subtraction programme was used. The subtracted images were transfered to a work station and using Brevis (Siemens Medical Solutions, Erlangen, Germany) software, time-signal intensity curves of breast lesions were acquired.

Three radiologists evaluated all images by consensus (E.D.A 15, E.P 11, S.Ü 7 years of experience). All the patients included to the study were assessed for tumor size, multicentricity and multifocality, contralateral lesions, chest wall involvement and lymphadenopathies. Tumor size classified by T staging: ≤2 cm T1, >2 cm ≤5 cm T2, >5cm T3, tumor of any size with chest wall or skin involvement T4. Lesion sizes were compared with histopathological results. Surgical procedures were noted for each stage. Patients who have two or more foci with type 3 curve or with irregular margins in the same quadrant with primary tumor accepted as having multifocal breast cancer. Having two or more foci with type 3 curve or with irregular margins in the other quadrants accepted as multicentricity. To assess kinetic features, ROI's (region of interest) were placed to the lesions (Figures 1 and 2). Findings were compared with postoperative histopathological findings.

Statistical Analysis

Statistical analyses were performed using "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)". Mean ± standard deviation [median (min-max)]

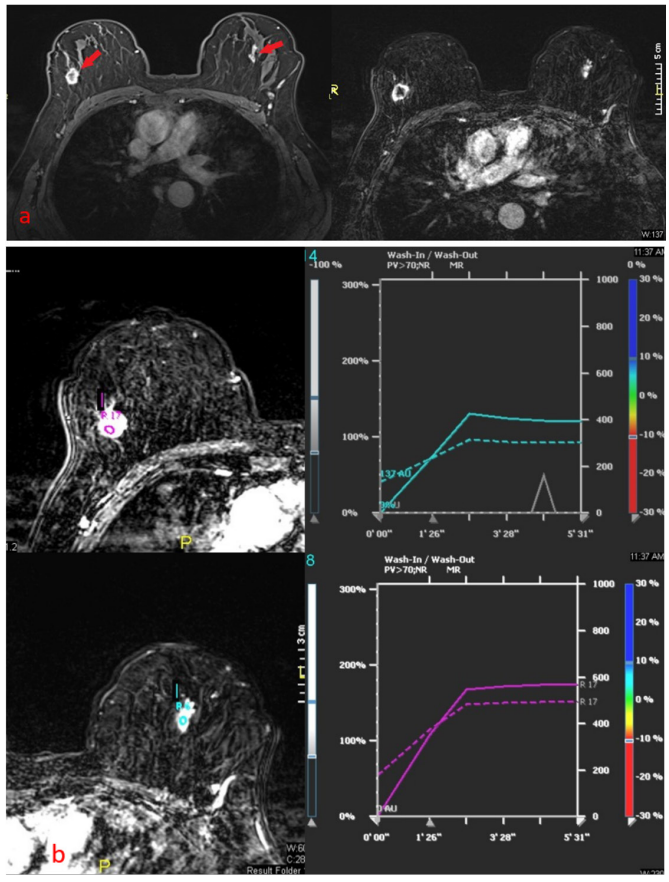

Figure 1: Bilateral breast cancer in 61-year-old patient. Dynamic contrast enhanced and subtracted images show a lesion in right breast with irregular contours and central necrosis and another lesion in left breast with irregular contours (a). Lesions have type 2 time-signal intensity curve (b)

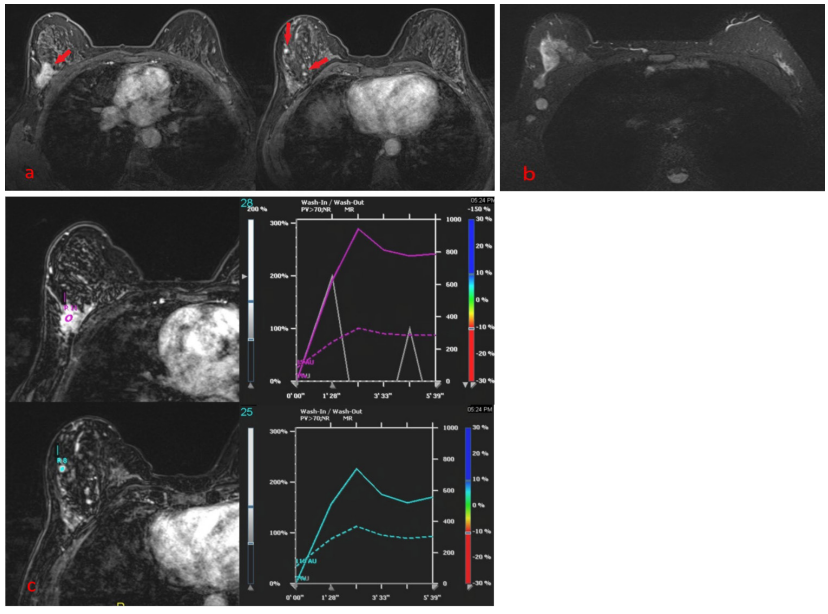

Figure 2: Right breast cancer in 42-year-old patient. Dynamic contrast enhanced images show large mass with irregular contours in upper-outer quadrant and multicentric foci in lower quadrant (a). Right axillary lymphadenopathies are seen (b). Primary and multicentric lesions have type 3 time-signal intensity curve (c)

and frequency (percent) were used as descriptive statistics. For evaluation of categorical variables pearson chi-square test and Fisher's exact test were used. Significant correlation was defined as $p<0.05$.

Results

Age range of the patients included to the study was 20-74 years (mean age 46 years).

Lesion sizes measured on MRI were changing between 3 mm and 65 mm (mean size 21 mm). The measurements on MRI were compared with histopathological results. Comparing with histopathological measurements a high reliability ratio (88%) was obtained.

42% of patients (n=13) had modified radical mastectomy (MRM), 42% of patients (n=13) had BCS and 16% of patients (n=5) had simple mastectomy. Eight patients had bilateral surgery. Out of 8 patients 2 had bilateral simple mastectomy, 1 had bilateral BCS, 1 had bilateral MRM, 2 had MRM and simple mastectomy and 1 had MRM and BCS. Comparing lesion sizes with surgical procedure 55% of T1 tumors (n=12) and 14% of T2 tumors (n=1) underwent BCS. Both of T3 tumors (n=2) and 86% of T2 tumors (n=6) underwent mastectomy (MRM or simple mastectomy) (Table 1). Among the patients with T1 tumor who had mastectomy (n=10), 2 were interpreted as multifocal and 1 as multicentric in MRI. Of these 10 patients, 4 were diagnosed with invasive lobular carcinoma.

Out of 31 patients 2 had multicentricity on MRI and they were proven histopathologically. MRI and pathology findings were statistically consistent ($p<0.001$). Ten patients' images were interpreted as multifocal. Two of these patients diagnosed as multifocal disease on pathological specimens. One patient whose images were not reported as multifocal had multifocal lesion on pathological specimens. In terms of multifocal focus, MRI and pathology findings were not statistically consistent ($p=0.180$). Six patients had contralateral suspicious lesions for malignancy. One of them diagnosed as contralateral tubular carcinoma. Out of 6 patients 2 had sclerosing adenosis, 2 had fibrocystic changes and 1 had lobular carcinoma in situ (LCIS) (Figure 3). Thirteen patients' images were reported positive for ipsilateral axillary lymphadenopathy. Twelve of these patients' pathological specimens showed metastasis in axillary lymph nodes. One patient without suspicion on MRI had axillary lymph node metastasis. For axillary lymph node involvement, MRI and pathology findings were statistically consistent ($p<0.001$). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are given in Table 2.

Table 1: Surgical methods according to tumor size (number of patients)

	T1	T2	T3	Total
BCS	12	1	0	13
Mastectomy	10	6	2	18
Total	22	7	2	31

BCS: Breast-conserving surgery

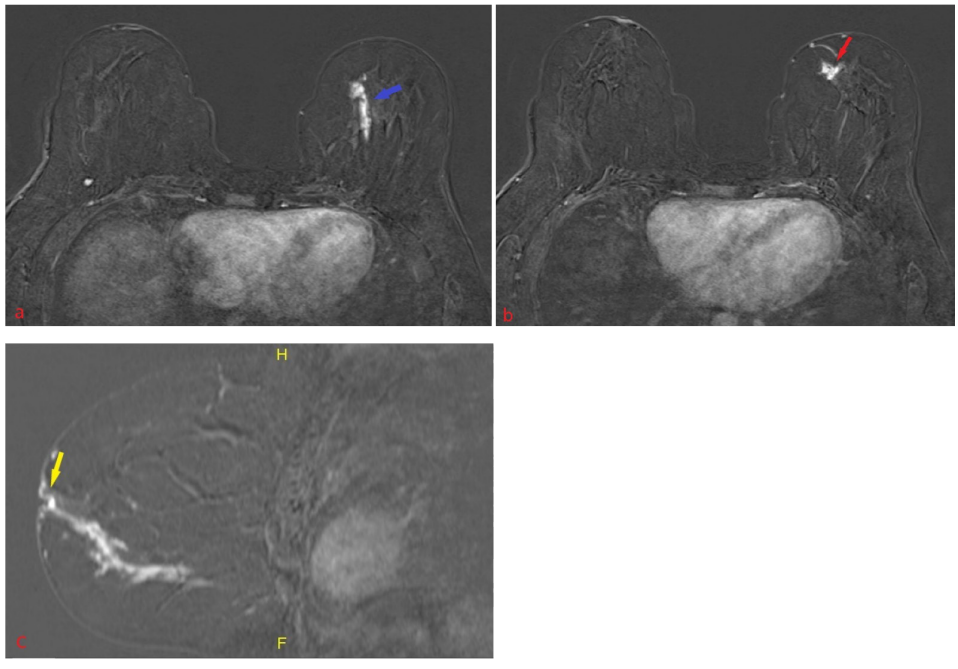

Figure 3: A contrast-enhancing lesion in the left breast (a). MRI shows irregular contours (red arrow) and papillary retraction (yellow arrow) which are indications of breast cancer (b and c). Histopathologic evaluation revealed fibrocystic changes

MRI: Magnetic resonance imaging

According to our results, NPV in detecting additional lesions and axillary lymphadenopathy with MRI were high.

One patient had a lesion that was suspicious but not obvious for pectoralis muscle invasion, but histopathology revealed no invasion.

All the patients evaluated as multicentric and seven of the patients evaluated as multifocal on MRI underwent mastectomy. Ten patients who had no suspicion for multicentricity or multifocality on MRI underwent mastectomy (Table 3). Four of them had invasive lobular carcinoma, 3 had DCIS, 1 had invasive ductal carcinoma, 1 had mucinous carcinoma and 1 had both invasive ductal carcinoma and contralateral tubular carcinoma. One of 2 patients with proven multicentricity was diagnosed as invasive lobular carcinoma and the other patient diagnosed as invasive ductal carcinoma. One of 3 patients with proven multifocality was diagnosed as invasive lobular carcinoma, 1 as invasive ductal carcinoma and 1 as DCIS.

All of patients (n=6) with invasive lobular carcinoma underwent mastectomy and 58% (n=11) of patients with invasive ductal carcinoma underwent BCS.

Discussion

Several studies showed that MRI increases the detection rate of tumor focus which cannot be found by conventional imaging methods. In a study made with 2610 women newly diagnosed with breast cancer, Houssami et al. (8) showed that the detection rate of additional focus with preoperative MRI was 16%. They claimed that detecting these foci can help to reduce locoregional recurrences, distant metastases and deaths. But, while doing that MRI can also cause false positive results. Houssami et al. (8) found the ratio of true positive results to false positive results as 1,9/1. They suggested that preoperative MRI can increase the number of unnecessary surgeries. 8,1% of patients eligible for BCS were treated with mastectomy because of additional focus detected on MRI. Wider excision or mastectomy was performed due to false positive results in 5,5% of patients. A multicenter study by Chou et al. (9) with 339 DCIS cases revealed that MRI could detect additional focus with 6.2% detection rate, while it had a 14.2% false-positive rate. In our study, the diagnosis of two patients with multicentric focus on MRI was confirmed histopathologically and they underwent MRM. Mastectomy was performed in 7 of 10 patients who were evaluated as multifocal on MRI. Five of 8 false positive patients had mastectomy due to suspicion of additional focus on MRI. It may suggest that 16,1% of all patients were treated with mastectomy to avoid missing multifocality.

In our study, the sensitivity and specificity of MRI in detecting multicentric focus were 100%. For multifocal focus the sensitivity was 67% and the specificity was 71%. Although the detection rate of additional foci which were actually present on MRI was high, the probability of false positive results was also high (PPV 20%, NPV 95%). While in terms of multicentric focus, MRI and pathology findings were statistically consistent, for multifocal focus, MRI and pathology findings were not statistically consistent.

Table 2: Sensitivity, specificity, PPV and NPV of MRI in detecting multicentric lesions, multifocal lesions, contralateral malignancy and axillary lymphadenopathy

	Multicentric lesions	Multifocal lesions	Contralateral malignancy	Axillary lymphadenopathy
True positive*	2	2	1	12
True negative**	29	20	25	17
False positive***	0	8	5	1
False negative****	0	1	0	1
Sensitivity (%)	100	67	100	92
Specificity (%)	100	71	83	94
PPV† (%)	100	20	17	92
NPV†† (%)	100	95	100	94

*Number of patients with true positive lesions
**Number of patients with true negative lesions
***Number of patients with false positive lesions
****Number of patients with false negative lesions
†Positive predictive value
††Negative predictive value
PPV: Positive predictive value, NPV: Negative predictive value, MRI: Magnetic resonance imaging

Table 3: Relationship between multifocality and surgical method (number of patients)

MRI	Surgery		Total
Multifocality	Mastectomy	BCS	
No	11	10	21
Yes	7	3	10
Total	18	13	31

MRI: Magnetic resonance imaging, BCS: Breast-conserving surgery

One of the factors affecting surgical planning is the tumor size. MRI determines the tumor size more accurately than ultrasonography (US) and mammography (5). In our study, lesion sizes measured on MRI and lesion sizes specified in pathological specimens were highly consistent. BCS was performed in 55% of patients with T1 tumor and it was similar with mastectomy rate. 89% of tumors bigger than 2 cm (T2 and T3) underwent mastectomy. Histopathological type of tumor and presence of additional focus might affected the surgical method in tumors smaller than 2 cm.

Assessment of contralateral breast is also important in preoperative evaluation. Patients with invasive lobular carcinoma, family history or BRCA gene mutation have an increased risk for contralateral breast cancer. Studies showed that in 1-18% of newly diagnosed patients, contralateral breast cancer which cannot be detected clinically or with conventional methods can be found with MRI. But, MRI can also lead additional invasive procedures because of false positive results (11). In a study of Brennan et al. (12) including 3253 women diagnosed with invasive breast cancer, in 9.3% of patients contralateral suspicious lesions seen only with MRI were detected. Less than half of these patients diagnosed as contralateral breast cancer and PPV was 47.9%. Ten women with suspicious contralateral MRI underwent contralateral mastectomy and just 3 of them diagnosed as cancer, 7 had benign changes. In our study, 8 patients underwent bilateral surgery and 6 of these patients had suspicious lesions on MRI. Prophylactic surgery was performed to one of the other two patients because of invasive lobular carcinoma diagnosis and to the other patient because of clinical suspicion. Just 1 of 6 patients diagnosed as contralateral invasive cancer (tubular carcinoma) and none of the patients without suspicious lesion on MRI had contralateral breast cancer histopathologically. In terms of detecting contralateral breast cancer with MRI, sensitivity, specificity, PPV and NPV were 100%, 83%, 17% and 100%, respectively. Out of 5 patients 1 had fibroadenoma, 1 had fibrocystic changes, 2 had sclerosing adenosis and 1 had lobular carcinoma in situ (LCIS). Preoperative biopsies may help to reduce unnecessary surgeries for suspicious contralateral lesions.

The axillary lymph nodes are the most common metastatic sites for breast cancer. Axillary lymph node involvement is important for staging and deciding whether or not to give adjuvant treatment (1). Sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) can be applied to patients with breast cancer. Although SLNB is a less invasive method, it may cause complications like lymph edema, pain, paresthesia, strength loss and stiffness (13). In 60% of newly diagnosed breast cancer patients lymph nodes are pathologically negative and SLNB is not useful for them. For that reason, to reduce axillary lymph node interventions which cause complications, it is aimed to develop non-invasive methods to make nodal staging. But, sensitivity and NPV of these methods should not be lower than SLNB (14). Non-invasive methods such as physical examination, US and PET/BT have low sensitivity and NPV. Sensitivity and NPV are indicated as 25-35.5% and 81.7% for physical examination, as 43.5-72.3% and 81.6-83.3% for US, as 56-62.7% and 79% for PET/BT (15). According to results of Kuijs et al. (14) compiling 16 studies, for axillary lymph node involvement sensitivity and NPV of MRI were reported as 84.7% and 95%, respectively. In our study, 12 of 13 patients with suspicious findings for lymph node metastasis on MRI had positive results pathologically. Although there were no suspicious findings on MRI, axillary lymph node metastasis was detected pathologically in 1 patient. Sensitivity was 92%, specificity was 94%, NPV was 94% and PPV was 92% in our study and in terms of sensitivity and NPV our results were consistent with previous studies. For axillary lymph node involvement, MRI and pathology findings were statistically consistent ($p<0.001$).

Histopathologic type of the breast cancer is a factor that determines the risk of additional focus and contralateral cancer. Therefore, the histopathologic type of tumor affects the surgical method. For invasive lobular carcinoma the risk of multicentricity, multifocality and contralateral cancer are higher than invasive ductal carcinoma (16). In a study of Mann et al. (17) MRI detected conventionally undetectable additional focus in 32% of patients and contralateral cancer in 7% of patients. They suggested that MRI changed the type of surgical treatment in 28% of patients with invasive lobular carcinoma. In our study, 1 of 2 patients with multicentricity and 1 of 3 patients with multifocality diagnosed as invasive lobular carcinoma.

There are some major limitations of our study. Because of the retrospective study design and being a single center study, patient population is small, which may affect the statistics and results. Detecting no significant difference in between histopathologic types for additional focus may be related to small number of patients included to the study and small number of patients with additional focus diagnosed pathologically. Comparing histopathologic type and surgical methods, it was noticed that all patients with invasive lobular carcinoma underwent mastectomy. Only 33% of these patients had suspicious findings for additional focus on MRI. The diagnosis of invasive lobular carcinoma was effective in decision of mastectomy for other patients. Half of patients with invasive lobular carcinoma underwent bilateral surgery and only 33% of them had suspicious contralateral lesion on MRI.

In conclusion, breast MRI has high NPV for multicentric/multifocal/contralateral lesions and axillary lymphadenopathies. It has an important role in preoperative assessment of breast cancer, determining tumor size correctly, excluding presence of additional focus and evaluating axillary lymph

node involvement. It should be considered that in detection of additional foci, MRI may cause false positive results and histopathological correlation should be provided before surgery.

Ethics

Ethics Committee Approval: The Institutional Review Board of Ankara University Faculty of Medicine approved this retrospective study protocol (approval no: 19-798-15, date: 11.12.2015).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Ü., E.D.A., E.P., İ.E., U.S., Design: S.Ü., E.D.A., E.P., İ.E., U.S., Data Collection and Processing: S.Ü., E.D.A., E.P., Analysis or Interpretation: S.Ü., E.D.A., E.P., İ.E., U.S., Literature Search: S.Ü., E.D.A., E.P., Writing: S.Ü., E.D.A., E.P.

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